Complete versus partial preservation of mitral valve apparatus during mitral valve replacement: meta-analysis and meta-regression of 1535 patients

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INTRODUCTION

Rationale

Despite the fact that existing evidence advocates the preservation of the mitral apparatus during mitral valve replacement (MVR), it is not performed routinely. Surgeons are refractory to using preservation techniques because a possible left-ventricular outflow obstruction may occur as preserved tissue interferes with prosthetic function, mainly in patients with septal hypertrophy undergoing anterior leaflet preservation [1].

Yun et al. [2] suggest that complete chordal preservation during MVR confers a significant advantage to the patient by reducing left ventricle chamber size and systolic afterload and minimizing any early postoperative drop in ejection fraction performance. Conversely, resection of the anterior chordae during MVR results in augmented systolic left ventricle afterload, thereby reducing pump performance, i.e. a larger decline in long-axis fractional shortening and ejection fraction and an increase in end-systolic volume.

Recently, we published a new meta-analysis [3] suggesting that surgeons should perform, as much as possible, the preservation of mitral apparatus and use techniques to avoid and/or eliminate the problem of left-ventricular outflow obstruction. We demonstrated that patients who underwent MVR with the preservation of the mitral valve apparatus (partial or complete) experienced less risk of death (30-day and 5-year follow-ups) and postoperative low cardiac output syndrome (LCOS).

Despite this fact, our meta-analysis did not establish whether there is any difference between complete and partial preservation (PP) during MVR, as this issue was an area to be addressed in this new meta-analysis.
**Objectives**

We performed a meta-analysis of studies to compare complete (MVR-CP) vs partial (MVR-PP) preservation of the mitral valve apparatus during MVR, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [4].

**METHODS**

**Eligibility criteria**

Using the Population, Intervention, Comparison, Outcome, Study (PICOS) strategy, studies were considered if: (i) population comprised patients undergoing MVR; (ii) compared outcomes between MVR-CP vs MVR-PP; (iii) outcomes studied included 30-day mortality, postoperative LCOS, 5-year mortality or left ventricle ejection fraction (LVEF) before and after surgery and (iv) were prospective or retrospective or randomized or non-randomized studies.

**Information sources**

The following databases were used (until July 2012): MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL/CCTR), ClinicalTrials.gov, SciELO (Scientific Electronic Library Online), LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde—The Latin American and Caribbean Health Sciences), Google Scholar and reference lists of relevant articles.

**Search**

We conducted the search using Medical Subject Heading (MeSH) terms 'mitral disease' OR 'mitral stenosis' OR 'mitral regurgitation' OR 'mitral insufficiency' OR 'mitral valve disease' OR 'mitral valve prolapsed' AND 'mitral valve replacement' OR 'mitral valve surgery' OR 'heart valve prosthesis implantation' AND 'preservation of subvalvular apparatus' OR 'preservation of chordae tendineae' OR 'chordal-sparing'.

**Study selection**

The following steps were done: (i) identification of titles of records through databases searching; (ii) removal of duplicates; (iii) screening and selection of abstracts; (iv) assessment for eligibility through full-text articles and (v) final inclusion in study.

One reviewer followed the Steps 1–3. Two independent reviewers followed step 4 and selected studies. Inclusion or exclusion of studies was decided unanimously. When there was disagreement, a third reviewer took the final decision.

**Data items**

The primary endpoint was the odds ratio (OR) for 30-day mortality after MVR-CP or MVR-PP. Secondary endpoints were the OR for postoperative LCOS, 5-year mortality and LVEF before and after surgery.

**Data collection process**

Two independent reviewers extracted the data. When there was disagreement about data, a third reviewer (the first author) checked the data and took the final decision on it. From each study, we extracted patient characteristics, study design and outcomes (number of events and number of total groups). When possible, actual probabilities of mortality after 5-year following MVR-CP or MVR-PP were used to calculate ORs. Alternatively, probabilities of mortality were estimated from published Kaplan–Meier survival curves.

**Risk of bias in individual studies**

Included studies were assessed for the following characteristics: design (prospective or retrospective), presence of randomization (yes or no), multicentre enrolment (yes or no), characteristics of participants (selection bias), characteristics of personnel (performance bias), outcome assessment (detection bias), incomplete outcome data addressed (attrition bias) and match adjustment (yes or no).

Two independent reviewers assessed risk of bias. Agreement between the 2 reviewers was assessed using $\chi^2$ statistics for full-text screening, and rating of relevance and risk of bias. When there was disagreement about risk of bias, a third reviewer (the first author) checked the data and took the final decision on it.

**Summary measures**

The principal summary measures were ORs with 95% confidence interval (CI) – for categorical variables (30-day mortality, post-operative LCOS and 5-year mortality); difference means and standard error (SE) – for continuous variables (LVEF before and after surgery); and $P$ values (that will be considered statistically significant when <0.05). The meta-analysis was completed using the software Comprehensive Meta-Analysis version 2 (Biostat, Inc., Englewood, NJ, USA).

**Synthesis of results**

Forest plots were generated for graphical presentations for clinical outcomes and we performed the $I^2$ test and $\chi^2$ test for assessment of heterogeneity across the studies [5]. Each study was summarized by the OR for MVR-CP compared with MVR-PP. The ORs were combined across studies using the weighted DerSimonian–Laird random effects model [6]. The model was weighted by the number of events in each study. The same procedure was executed for continuous variables, taking into consideration the difference in means.

**Risk of bias across studies**

There is a tendency or researchers, editors of medical journals and pharmaceutical companies to handle the reporting of
experimental results that are ‘positive’ (i.e. showing a significant finding) differently from results that are negative (i.e. supporting the null hypothesis) or inconclusive, leading to a misleading bias in the overall published literature, which generates the publication bias. To assess publication bias, a funnel plot was generated (for primary endpoint), which was statistically assessed by Begg and Mazumdar’s test [7] and Egger’s test [8].

Meta-regression analysis

Meta-regression analyses were performed to determine whether the effects of MVR-CP were modulated by prespecified factors. Meta-regression graphs describe the effect of CP on the outcome (plotted as a log OR on the y-axis) as a function of a given factor (plotted as a mean or proportion of that factor on the x-axis). Meta-regression coefficients show the estimated increase in log OR per unit increase in the covariate. Since log OR > 0 corresponds to OR > 1 and log OR < 0 corresponds to OR < 1, a negative coefficient would indicate that as a given factor increases, the OR decreases.

The predetermined modulating factors to be examined were: sex, age, left ventricle function. Sex was represented as the proportion of males in the study. Age was represented as the mean age of the patients participating in the study. Left ventricle function was represented as the mean ejection fraction (%) measured by echocardiography.

RESULTS

Study selection

A total of 798 citations were identified, of which 34 studies were potentially relevant and retrieved as full-text. Eight publications fulfilled our eligibility criteria [2, 9–15]. Interobserver reliability of study relevance was excellent (κ = 0.86). Agreement for decisions related to study validity was very good (κ = 0.81). The search strategy can be seen in Fig. 1.

Study characteristics

Characteristics of each study are given in Table 1. A total of 1535 patients were studied, with 597 receiving MVR-CP and 938 receiving MVR-PP, including the years 1990–2011. Six studies were of mixed mitral pathology; one involved only rheumatic mitral disease and one was about chronic insufficiency. Four studies
were prospective, two were randomized and all were single centre. The overall internal validity was moderate and is illustrated in Table 2.

Synthesis of results

The OR of the risk of 30-day mortality in the MVR-CP group compared with the MVR-PP group in each study is reported in Fig. 2A. There was no evidence for important heterogeneity of treatment effect among the studies for 30-day mortality. The overall OR (95% CI) of 30-day mortality showed no statistically significant difference for MVR-CP compared with MVR-PP (random effect model: OR 0.87, 95% CI 0.50–1.52 and \( P = 0.63 \)).

The OR of the risk of postoperative LCOS in the MVR-CP group compared with the MVR-PP group in each study is reported in Fig. 2B. There was evidence for important heterogeneity of treatment effect among the studies for LCOS. The overall OR (95% CI) of postoperative LCOS showed no statistically significant difference for MVR-CP compared with MVR-PP (random effect model: OR 0.35, 95% CI 0.11–1.08, \( P = 0.07 \)).

The OR of the risk of 5-year mortality in the MVR-CP group compared with the MVR-PP group in each study, is reported in Fig. 2C. There was no evidence for important heterogeneity of treatment effect among the studies for 5-year mortality. The overall OR (95% CI) of 5-year mortality showed no statistically significant difference for MVR-CP compared with MVR-PP (random effect model: OR 0.70, 95% CI 0.43–1.14; \( P = 0.15 \)).

The standard difference in means for LVEF before and after MVR-CP in each study is reported in Fig. 3A. There was evidence for important heterogeneity of treatment effect among the studies for this variable. The overall difference in means (95% CI) of LVEF before and after MVR-CP showed no difference (random effect model: 0.52, SE 0.51, 95% CI \(-0.19–1.24\); \( P = 0.31 \)).

The standard difference in means for LVEF before and after MVR-PP in each study is reported in Fig. 3B. There was evidence for important heterogeneity of treatment effect among the studies for this variable. The overall difference in means (95% CI) of LVEF before and after MVR-PP showed no difference (random effect model: 0.06, SE 0.35, 95% CI \(-0.62–0.74\); \( P = 0.86 \)).

The standard difference in means for change in LVEF before and after MVR-CP or MVR-PP in each study is reported in Fig. 3C. There was evidence for important heterogeneity of treatment effect among the studies for this variable. The overall difference in means (95% CI) of changing in LVEF before and after MVR-CP or MVR-PP showed no difference between groups (random effect model: \(-1.48\), SE 1.89, 95% CI \(-5.17–2.22\); \( P = 0.43 \)).

Risk of bias across studies

Funnel plot analysis (Fig. 4) disclosed symmetry around the axis for the treatment effect in primary endpoint, which means we probably do not have publication bias.
Meta-regression analysis

Meta-regression coefficients were not statistically significant for primary endpoint and proportion of males, mean age or LVEF, which means that they do not modulate the effect of MVR-CP (see Fig. 5).

DISCUSSION

Summary of evidence

The results of this meta-analysis demonstrate that there was no statistically significant difference in favour of MVR-CP compared with MVR-PP in OR for 30-day mortality, postoperative LCOS and 5-year mortality, these summary measures free from the influence of heterogeneity of the effects (except postoperative LCOS) or publication bias. Taking into consideration LVEF, neither MVR-CP nor MVR-PP demonstrated a statistically significant improvement in LVEF before and after surgery, and both strategies were not different from each other, but these results were under the important influence of heterogeneity of the effects.

Considerations about this meta-analysis

To our knowledge, this is the first meta-analysis of studies performed to date on comparison between MVR-CP and MVR-PP, providing incremental value by demonstrating that MVR-CP (technically more-difficult surgery) is not superior to MVR-PP (technically less-difficult surgery) in terms of hard outcomes.
The choice of which mitral apparatus preservation technique to use ultimately depends upon the individual patient and surgeon. Factors to be considered are the simplicity and reproducibility of the technique, as well as the anatomical and pathological characteristics of the mitral valve and the degree of left-ventricular dysfunction. Despite the fact that existing evidence advocates subvalvular apparatus preservation, it is not performed routinely. Surgeons are reluctant to use CP techniques arguing that left-ventricular outflow obstruction may occur as preserved tissue interferes with prosthetic valve function. It has also been reported that some of the preservation techniques may cause alterations of the left-ventricular geometry, resulting in rupture of the papillary muscles, systemic embolization, or dehiscence of mitral leaflets from the transposed position, emphasizing the risk of left ventricle outflow obstruction in patients with septal hypertrophy undergoing anterior leaflet preservation [1]. Surgeons should also take into consideration that systolic anterior motion of the retained anterior mitral leaflet can occur [16-19], also contributing to left-ventricular outflow obstruction.
Interestingly, we demonstrated in the present meta-analysis that there is no statistically significant improvement in LVEF after surgery in comparison with preoperative measures (neither MVR-CP nor MVR-PP) and there is no difference in terms of postoperative changes in LVEF between groups. Since we demonstrated in a previous meta-analysis [3] that patients who underwent MVR with any preservation of the mitral valve apparatus (partial or complete) experienced less risk of death (30-day and 5-year follow-ups) and postoperative LCOS, we could think that these benefits are independent of the performed technique of preservation (partial or complete) and independent of changes in LVEF after surgery.

In this situation, a question seems to be important: if the total preservation of subvalvular mitral apparatus technique is associated with the appearance of an important complication (left-ventricular outflow obstruction) and if it does not present any benefit (in terms of hard outcomes and in terms of LVEF) compared with the PP technique, should we not prefer the latter (for being a simpler technique)?

Risk of bias and limitations

There are inherent limitations with meta-analyses, including the use of cumulative data from summary estimates. Patient data were gathered from published data, not from individual patient follow-up. Access to individual patient data would have enabled us to conduct further meta-regression analysis and propensity analysis to account for differences between the treatment groups.

The studies included were of varying design, ranging from prospective randomized to retrospective studies. Only two studies were randomized, and there is an important problem about the definition of 'randomized'. All randomized studies did not describe the process of randomization, which makes us wonder if the samples are truly randomized. The two studies also did not describe how blind they are (single, double and triple), which can generate significant performance and detection biases. There was a variation in selection criteria used by individual surgeons to allocate patients to each group in each study and the two groups were not always fully matched for important risk factors. This meta-analysis included data from non-randomized observational studies, which reflects the 'real world', but they are limited by treatment bias, confounders and a tendency to overestimate treatment effects. Patient selection alters outcome and thus makes non-randomized studies obviously less robust.

Unfortunately, only one study reported that the rate of postoperative left-ventricular outflow obstruction [13] was 0%. It would be interesting to know these rates of left-ventricular outflow obstruction in each study and whether there was any difference between MVR-CP and MVR-PP.

Another limitation is the heterogeneity of the strategies across the studies. Among the studies used in this meta-analysis, we identified many different techniques of bileaflet and/or posterior leaflet preservation. This aspect may influence in the results.

CONCLUSIONS

We found evidence that argues against any superiority of CP of the mitral valve apparatus during MVR in comparison with PP in terms of hard outcomes.

Conflict of interest: none declared.
REFERENCES